DRAWINGS

Drawings 3, 4, and 14-21 are objected to for poor quality. Drawings 2, 3, 4, 6, 7, 8, 9, 12, 20, and 21 are objected to as not labeled separately or properly. Drawings 1-21 are objected to as not containing lines, numbers and letters that are uniformly thick and well defined, clean, durable and black. The replacement sheets attached hereto at tab 1 correct all of the aforementioned objections.

REMARKS

Applicant has amended claim 1 to more clearly recite the claimed model of macrostructural properties of a bone. Support for the amendment appears in paragraphs [0003], and [0038] to [0051]. Specifically, paragraph [0003] defines the first, second, and third orders of bone. Paragraphs [0039] to [0044] further describe the hierarchical levels/orders of compact bone. Paragraphs [0044] to [0049] describe the hierarchical levels/orders of cancellous bone. Paragraphs [0039], [0050], and [0051] describe the composition of the claimed model that respects the hierarchical structural and mechanical properties of a bone starting from the third order of bone microstructural components and proceeding to the first order of bone. Other amendments are editorial and are made for clarity of expression. The amendment emphasizes that the claimed model is not a gross approximation of bone structure, does not broadly assume microstructural uniformity, e.g., of collagen bundles, and does not use assumptions of homogeneity at different orders of bone structure to estimate the interactions of bone with external force. Instead, the claimed model includes the hierarchical structural and hierarchical mechanical properties of the components of bone from the third order to the first order of bone, thus accounting for the non-homogeneity of bone, as well as the dynamic interactions of the components of bone with external force.

Applicant also adds new claims 6 through 9. Support for claim 6 appears in paragraphs [0052] to [0054], [0082], [0086] to [0088], and [0090] to [0092]. Support for new claim 7 appears in paragraphs [0055] to [0056], and [0090]. Support for new claim 8 appears in paragraphs [0055] to [0057], and [0090]. Support for new claim 9 appears in paragraphs [0084], [0085], and [0090].

35 U.S.C. §103(a)

A. Crolet and Manolagas

Claim 1 stands rejected under 35 U.S.C. §103(a) as obvious over Crolet in view of U.S. Patent No. 6,416,737 to Manolagas ("Manolagas").

Applicant respectfully traverses this rejection.

Crolet teaches an unrealistic and oversimplified model of bone because it disregards the non-homogeneity of the structure (p. 679). Specifically, Crolet teaches a theory of bone macrostructure which presumes there are uniform collagen fibrils per osteon, resulting in an entire osteon that is homogenous and isotropic (not direction dependent), i.e., a simple average. Crolet also assumes that collagen fiber and hydroxyapatite are homogeneous, isotropic, and linearly elastic (p. 679, col. 1, para. 3). Crolet further assumes collagen to be perfectly embedded in hydroxyapatite without lacunae and with a rigid interface (p. 679, col. 1, para. 3).[1] Based upon these assumptions, Crolet calculates the elasticity tensor of one sector, i.e., one lamella, and expands this homogenized estimation to characterize behavior of all lamellar sectors (pp. 679-680). Crolet also uses assumed homogeneous properties to simulate groups of osteons which are not homogeneous (pp. 680-681). This is a poor model because homogeneous groups of osteons cover only a small region of an actual bone. Crolet also does not assemble groups of osteons into a model of macroscopic properties of an entire bone, e.g., a femur. Accordingly, Crolet disregards the dynamic hierarchy of bone structure because it makes unrealistic estimates of structure (e.g., "averaging" osteon structure) and mechanical properties (e.g., assuming linear elasticity). The lack of recognition and use of the hierarchical structural and mechanical properties limits the Crolet model, and is quite different from the invention as claimed.

Manolagas does not cure the deficiencies in Crolet. Manolagas does not suggest including properties of the microstructure or the interactions of bone with external force into a macrostructural model of bone. Instead, this reference discloses increasing bone strength by administration of a bisphosphonate, a widely used drug to treat osteoporosis (see Manolagas, Abstract). Furthermore, while the Office Action contends that Manolagas teaches a model comprising interactions of the bone with external force, the portions of Manolagas cited in the Office Action merely recite the truism that bone structures of humans and other vertebrates are

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[1] Later publications show that Crolet's assumptions are incorrect. See Ascenzi, M-G., "*A first estimation of prestress in so-called circularly fibered osteonic lamellae*," 32 J. Biomechanics 935-942, at 941 (Tab 2) ("Ascenzi 1999"). Ascenzi 1999 discloses a model of a "bright" lamella and demonstrates that bright lamella cannot consist entirely of transverse collagen bundles (as in Crolet), but oblique bundles need to be present as well.

"permanently distorted by the application of external forces" (Manolagas col. 2, ll. 32-36). Manolagas in no way suggests including orders of hierarchy, corresponding properties, or the microstructural characteristics of bone with external force into a model of macrostructural properties of bone as in claim 1.

Manolagas provides no suggestion or motivation to modify what is taught in Crolet to arrive at the claimed invention by teaching the administration of bisphosphonates to increase bone strength. No mention is made of modeling bone. Alone or together, Crolet and Manolagas do not disclose inclusion of a complete "hierarchical structure and hierarchical mechanical properties of microstructure of bone" into a model, nor do they include the behavior of bone in response to external forces. Crolet and Manolagas further do not delineate the first, second, and third orders of bone wherein each component of the orders is "correlated with at least one mechanical property," and where "components of the third order are assembled to provide a description of components of the second order, and components of the second order are assembled to provide a description of one or more characteristics of the first order, including at least one interaction with an external force." Accordingly, the model of claim 1 is not obvious over Crolet in view of Manolagas.

B. Crolet, Manolagas, and Jiang

Claims 2 and 4 stand rejected under 35 U.S.C. §103(a) as obvious over Crolet in view of Manolagas and further in view of U.S. Patent No. 6,442,287 to Jiang ("Jiang"). The Office Action contends that Crolet and Manolagas teach the model of claim 1 and a method of using the model, and further that Jiang teaches that bone is cancellous bone and a method of predicting deformation and fractures of cancellous bone using the model.

Applicant respectfully traverses this rejection.

Applicant concedes that Jiang teaches that bone includes cancellous bone; however, Crolet in view of Manolagas and further in view of Jiang in no way suggest the desirability and thus the obviousness of making the claimed model of cancellous bone. Bone is a heterogeneous medium with a multiscale composite structure that is anisotropic (i.e., direction dependent). However,

further to the arguments regarding Crolet above, Crolet over-simplifies bone with a homogenous approximation of microscopic mechanical characteristics, and assumes isotropy, to arrive at macroscopic bone behavior; while Manolagas merely teaches bisphosphonate administration. Jiang teaches a method and system for the computerized analysis of bone mass and structure to estimate bone strength based upon digital images of bone, and further based upon a measure of bone mineral density, a Minkowski dimension, e.g., a measure of bone geometry, a trabecular orientation, and subject data. None of these references suggest the desirability of accounting for the hierarchical structural and mechanical properties of microstructure and interactions of bone with external force to provide a model of the macrostructural properties of bone. The combination of these references does not suggest or achieve the novel model "comprising hierarchical structural and hierarchical mechanical properties of microstructure of [cancellous] bone and interactions of said bone with external force" as in claim 2.

The combination of Crolet, Manolagas, and Jiang also do not provide the method recited in claim 4 of predicting deformation and fractures of bone using the model of claim 1. Indeed Jiang deals with deformation and fractures, but not in the manner claimed here. Jiang's model is based on digital images to determine bone mineral density (BMD) and further estimate strength of bone based upon BMD, a mathematical calculation of bone geometry based upon the image, and trabecular orientation (see Jiang, Abstract). Like Crolet, these are gross properties and oversimplified estimates. It would not have been obvious to one of skill in the art to arrive at the method of claim 4 of predicting deformation and fractures using the claimed model of macrostructural properties of bone based upon the disclosure in Crolet, Manolagas, and Jiang.

Accordingly, claims 2 and 4 are not obvious over Crolet in view of Manolagas and further in view of Jiang.

C. Crolet, Manolagas, Winder, Ascenzi I to IV

Claim 3 stands rejected under 35 U.S.C. §103(a) as obvious over Crolet in view of Manolagas; and further in view of U.S. Patent No. 6,213,958 to Winder ("Winder"); Ascenzi, "The

tensile properties of single osteons," August 1965 ("Ascenzi I"); Ascenzi, "The shearing properties of single osteons," September 1971) ("Ascenzi II"); Ascenzi, "The torsional properties of single selected osteons," October 1993 ("Ascenzi III"); and Ascenzi, "Pinching in longitudinal and alternate osteons during cyclic loading," November 1996 ("Ascenzi IV"). The Office Action contends that Crolet and Manolagas teach the method of claim 1, and that Winder and Ascenzi I to IV teach all of the mechanical properties in claim 3.

Applicant respectfully traverses this rejection.

Crolet in view of Manolagas do not teach the model of claim 3 because as noted above, Crolet teaches an over simplified hierarchical approximation of bone, and does not account for hierarchical structural and mechanical properties of microstructure and interactions of bone with external force. Further, the addition of Winder and Ascenzi I to IV do not render claim 3 obvious even though these references mention mechanical properties of bone.

Winder discloses a data acquisition system and method comprising an array of wideband transducer sensors for measuring tissue surface vibrations in skin, a wideband recorder, a processing means, and a signal processor for classifying a bone feature such as architectural integrity, fatigue strength and bone quality. Winder recognizes that bone is anisotropic, and that the mechanical properties of bone, e.g., strength, toughness, and structural adaptation, depend on bone architecture at the microscopic and macroscopic level (Winder, col. 10, ll. 63-67). However, Winder does not account for, nor does Winder teach, that the mechanical properties of bone also vary with respect to the discrete hierarchical levels of bone architecture. Instead, Winder discloses a processing method that is sensitive to the structural changes in bone architecture, but only sensitive to the <u>macro-mechanical</u> properties of bone (col. 4, lines 45-48). Furthermore, Winder does not disclose what level or order of microstructure it is able to detect, and whether its data acquisition system actually accounts for the third order of bone, e.g., collagen bundles, hydroxyapatite crystallites, mucopolysaccharides, and combinations thereof, or even the non-homogenous second order of bone. Thus, while acknowledging that bone has microstructural properties which are not

homogeneous or isotropic, Winder does not make use of this information to provide a model as claimed.

Ascenzi I discloses a quantitative investigation of the tensile deformation of single osteons from human and ox femoral shafts using a microwave extensimeter (see Ascenzi I, p. 375, col. 1, second paragraph). Ascenzi II discloses an investigation of the shearing strength of single human osteons using a microtesting machine (see Ascenzi II, Abstract). Ascenzi III discloses an investigation of the mechanical behavior of fully calcified longitudinal and alternate osteons loaded by torsion along their axis (see Ascenzi III, Abstract). Ascenzi IV discloses an investigation of the degrading phenomenon "pinching" during cyclic loading of materials of fully calcified longitudinal and alternate osteons (see Ascenzi IV, Abstract). These are measurements of mechanical properties, but they are not employed to provide a hierarchical model of bone, nor is there a suggestion to do so.

It would not have been obvious to modify the model of Crolet with the findings of Winder and Ascenzi I to IV. Crolet teaches simulation of mechanical behavior of all lamellae by "knowledge of the homogenized characteristics of only one [lamellae]" (Crolet, p. 680, col. 1, para. 4). Crolet further discloses simulation of osteon structure by using "only the mathematical theory of homogenization" (p. 680, col. 1, para. 5). This teaches <u>away</u> from the invention. Crolet makes no suggestion to modify its simplified mathematical model by inclusion of mechanical properties, e.g., tension and prestress, shearing strength, torsional properties, and pinching. Crolet offers its mathematical approach as sufficient to create a partial macrostructural model of bone, and thus would not teach one skilled in the art to incorporate any practical measurements of experimental conditions, nor any conclusions reached by Ascenzi I to IV (e.g., regarding the implications of calcium content and osteons having longitudinal arrangement versus osteons having alternate arrangement). Furthermore, the addition of Winder, would not teach one skilled in the art to account for the hierarchical mechanical properties of each level of bone, and correlate such mechanical properties with each component of the hierarchical structure of bone as claimed.

The rejection of claim 3 over the seven references is apparently based upon hindsight afforded by the claimed model incorporating mechanical properties such as "tension, compression, shear, bending, torsion, prestress, pinching, and cement line slippage." The combination of references do not suggest the desirability and thus the obviousness of claim 3 as a whole because the instant claim solves the problem in the art resulting from prior art bone models that assume that bone is homogenous, and isotropic, and attempt to predict structure based upon mathematical models alone. The taking of measurements in the secondary references does not lead to the claimed model here. Accordingly, claim 3 is not obvious over the combination of Crolet, Manolagas, Winder, and Ascenzi I to IV.

D. Crolet, Manolagas., Copland III, and Agrawal

Claim 5 stands rejected under 35 U.S.C. §103(a) as obvious over Crolet in view of Manolagas, and further in view of U.S. Patent Nos. 6,333,313 to Copland III ("Copland III") and 5,947,893 to Agrawal ("Agrawal"). The examiner contends that Crolet and Manolagas teach the model of claim 1, that Copland teaches a method of identifying the requirements of bone reconstruction, and that Agrawal teaches a method of identifying the requirements of prosthesis.

Applicant respectfully traverses this rejection.

Claim 5 recites a "method of identifying the requirements of bone reconstruction and prosthesis using the model" in claim 1. This claim is not obvious over the combination of Crolet, Manolagas, Copeland III, and Agrawal. One skilled in the art would not arrive at the claimed method based upon these references. The combination of teachings of Crolet (an over-simplified and highly unrealistic bone model), with Manolagas (bisphosphonate administration), Copeland III (oxytocin administration), and Agrawal (a method of making a porous prosthesis) in no way suggest the desirability or systematic steps, and thus the obviousness, of the claimed method incorporating use of a model of the macrostructural properties of a bone, respecting hierarchical structure, hierarchical mechanical properties of microstructure, and interactions of bone with external force. The combination of cited references would at most provide a method for making an unrealistic bone

model of a porous prosthesis combined with bisphosphonate and oxytocin administration. The cited combination does not achieve the invention, and at best is based upon hindsight. Accordingly, claim 5 is not obvious over the cited references and Applicant respectfully requests withdrawal of this rejection.

In view of the above remarks, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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Attachments